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(54) Title: TOPICAL TREATMENT OF DIABETES WITH INSULIN AND PENETRANT ENHANCER APPLIED TO THE SKIN AND COVERED BY A PATCH

(57) Abstract

A composition, which when applied to the surface of the skin of a diabetic subject is useful for treating diabetes, includes a first layer in contact with the skin surface and a second layer covering the first layer. The first layer contains an effective amount of insulin for treating diabetes, an effective enhancing amount of a penetrant enhancer and a suitable carrier. The second layer comprises a suitable adherent, nonporous patch material. In a preferred embodiment, the first layer is in the form of a gel and includes a suitable gel material. Application of the composition to the surface of a diabetic subject's skin for a sufficient period of time to permit insulin present in the composition to cross the skin provides a method for treating diabetes.

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TOPICAL TREATMENT OF DIABETES WITH INSULIN AND PENETRANT ENHANCER APPLIED TO THE SKIN AND COVERED BY A PATCH

Background of the Invention

Exogenous insulin is the mainstay of therapy for human diabetics. A major disadvantage, however, is the necessity to administer the drug parenterally, e.g., with a needle and syringe. The need for at least daily injections of insulin is an important factor in patient compliance and comfort.

The ability of 15% aqueous DMSO to enhance transport of insulin across the bladder of dogs was described in 1964 [Jacob, S. et al., Fed. Proc. 23:410 (1964); Jacob, S. et al., Curr. Therapeutic Res. 6:134 (1964)]. See also U.S. Patent 3,551,554, issued December 29, 1970. In 1975, Kamhi-Danon and Stern [Kamhi-Danon, B and Stern, P., Acta. Pharmaceut. Jugoslav 25:51 (1975) noted that cutaneous administration of insulin in aqueous or dimethylsulfoxide solution produced characteristic insulin seizures in starving, normal mice. They observed that DMSO accelerated insulin effects when topically applied. There is little experience reported in the literature with topical application of insulin. Data available relate to case reports documenting hypoglycemia induced in patients with decubitus ulcers or open wounds, who were treated with topical applications of insulin to injured skin surfaces. [Coid, D., Br. Med. J. Oct. 22:1063 (1977); Rowe Van Ort, S. and Gerber, R. Nursing Res. 25:9 (1976) and Gerber, R. and Rowe Van Ort, S., Nursing Res. 28:16 (1979)].

Penetrant enhancers other than DMSO are known. [Dugard, P.H. and Scheuplein, J., Dermatol. 60:263 (1973); McCullough, J.L. et al., Dermatol. 66:103 (1976); U.S. Patent

3,952,099 (1976); U.S. Patent 3,527,864 (1970). Of these, n-decyl-methyl sulfoxide is approved for use in the topical treatment of acne.

Although the use of a simple mixture of insulin and a penetrant enhancer might be considered for use in treating diabetes, the difficulties inherent in using such a mixture, including inability to adequately control dosages, difficulty of maintaining material in contact with the skin for any length of time and less than desirable absorption rates necessitating use of large amounts of insulin, render such an approach unlikely to be of clinical value. In addition, prior work with penetrant enhancers and patching methods has been directed to the administration of molecules considerably smaller than insulin, i.e., molecules with much lower molecular weights.

The present invention overcomes these difficulties and provides a method for treating diabetes involving topical application of a composition to the surface of the skin of a diabetic subject.

Summary of the Invention

A composition, which when applied to the surface of the skin of a diabetic subject or patient is useful in the treatment of diabetes, comprises a first layer in contact with the skin surface and a second layer covering the first layer. The first layer includes an effective diabetes-treating amount of insulin, an effective enhancing amount of a penetrant enhancer such as dimethyl sulfoxide or n-decyl-methyl sulfoxide and a suitable carrier. The second layer comprises a suitable adherent, nonporous patch material such as polyethylene.

Preferably, the first layer is in the form of a gel and includes a suitable gel material such as hydroxymethyl cellulose, hydroxypropylmethyl cellulose or hydroxypropyl cellulose.

Application of the composition to the skin of a diabetic subject for a sufficient period of time to permit insulin present in the composition to cross the skin provides a method for treating diabetes.

Detailed Description of the Invention

This invention concerns compositions which when applied to the surface of a diabetic patient's or subject's skin are useful in treating diabetes.

In one embodiment such a composition includes a first layer in contact with the skin surface and a second layer covering the first layer. The first layer includes an effective diabetes-treating amount of insulin, an effective enhancing amount of a penetrant enhancer and a suitable carrier. The second layer comprises a suitable adherent, nonporous patch material.

Although the first layer may be formulated directly on the surface of the skin, it is generally preferable to first formulate the ingredients and then apply the formulated ingredients to the skin surface to form the layer.

Effective diabetes-treating amounts of insulin may vary from the amounts normally required for subcutaneous or intravenous therapy. However, in the practices of the present invention it is contemplated that the amounts will be similar to those presently employed in the other treatment modes since one unit of protamine zinc insulin administered subcutaneously is an appropriate dose for maintenance of relative normoglycemia in diabetic rodents [Andersson, A., Diabetologia 25:269 (1983)]. The form of insulin may also vary and includes regular insulin, NPH, Lente and protamine zinc insulin. It is contemplated that insoluble repository forms of insulin may have longer durations of action than regular insulin.

The penetrant enhancer may be any of a number of agents known to enhance the penetration and increase the absorption of

drugs across the skin. Examples include dimethyl sulfoxide, dimethyl acetamide, dimethylformamide and n-decyl-methyl sulfoxide. Additional such agents include propylene glycol, glycerin, lanolins, alcohols, anionic emulsifiers (e.g. sodium lauryl sulfate) and surfactants (nonionic emulsifiers such as polyoxyethylene fatty alcohol ethers and esters; polyoxyethylene fatty acid esters, e.g. polyoxyethylene stearate; polyoxyethylene sorbitan fatty acid esters and sorbitan fatty acid esters, e.g. sorbitan monostearate; polyoxyethylene glycol fatty acid esters; polyol fatty acid esters, e.g. glyceryl monostearate; and ethoxylated lanolin derivatives. [See also, Mullins, J., "Medicated Applications" in Remington's Pharmaceutical Sciences, 16th edition, Arthur Osol, editor, Mack Publishing Co. Easton, Pennsylvania (1980)]..

Of these penetrant enhancing agents the presently preferred agents are DMSO and the DMSO-related compounds including dimethylacetamide, dimethylformamide and most particularly N-decyl-methyl sulfoxide (NDMS). NDMS (0.125%) is FDA-approved in a 30% ethanol solution containing tetracycline for topical application in the treatment of acne (Topicycline™, Procter and Gamble Company, Cincinnati, Ohio).

N-decyl-methyl sulfoxide is at least 15 times more effective than DMSO in skin penetrance enhancement [McCullough, J.L. et al., J. Invest. Dermatol. 66:103 (1976)], and in a less than 1% solution, applied topically, in amounts less than 1.3 ml per day, is safe and without side effects [Physicians Desk Reference, Medical Economics Company, Oradell, New Jersey (1983)]. Substitution of NDMS for DMSO or lowering the amount of enhancing agent used is particularly desirable since DMSO has several undesirable, dose-related side effects. [Harter, J., Annals of the New York Academy of Sciences, Vol. 411, Ed., J.C. de la Torre, (1983), page 1;

Rubin, L. Ibid., p. 6; David, N., Ann. Rev. Pharmacol. 12:353 (1972); Calesnick, B., Clin. Pharmacol. 23:167 (1981)]. Topically applied DMSO, in concentrations above 50%, has been found to cause skin erythema, edema and pruritis with scaling of epithelium and troublesome skin irritation [Smith, E. et al., J. Clin. Pharmacol., Sept./Oct.:315 (1968); and Frosch, P. et al., Br. J. Dermatol. 102:263 (1980)].

Presently, DMSO in 50% aqueous solution is FDA approved for instillation in the bladder to treat interstitial cystitis [Stewart, B. et al., J. Urology 116:36 (1976)]. It is expected that biological effects of DMSO in penetrance enhancement of insulin transport across the skin, even at concentrations as low as 1-5% will be effective since Whitworth and Stevenson [J. Pharmaceut. Sci. 60:48 (1971)] documented increased absorption of atropine across the skin with these low concentrations of DMSO.

In the compositions of the present invention the amount of penetrant enhancer present in the first layer may vary over a wide range, depending upon the specific enhancer being used. In general, the amount will not exceed about 50% by volume of the first layer.

The first layer also includes a suitable carrier. One generally useful carrier is water, e.g., deionized distilled water. Other carriers include alcohols such as methanol or ethanol or aqueous mixtures thereof.

Alternatively, the carrier may be formulated in an emulsion or cream base. One such system is Hydrophilic Ointment USP, a widely available oil-in-water emulsion. (Table 1). Another such system is Hydrophilic Petrolatum USP, a water-and-oil emulsion (Table 2).

Table 1

Hydrophilic Ointment

Methylparaben	0.25 g
Propylparaben	0.15 g
Sodium Lauryl Sulfate	10.00 g
Propylene Glycol	120.00 g
Stearyl Alcohol	250.00 g
White Petrolatum	250.00 g
Purified Water	369.60 g
	1000.00 g

Table 2

Hydrophilic Petrolatum USP

Cholesterol	30.0 g
Stearyl Alcohol	30.0 g
White Wax	80.0 g
White Petrolatum	860.0 g
	1000.0 g

In addition to the carrier, the first layer may also include additional materials such as emulsifying agents, suspending agents, preservatives and the like.

In a preferred embodiment, the first layer is in the form of a gel. Suitable gel materials include hydroxymethyl cellulose, hydroxypropylmethyl cellulose or hydroxypropyl cellulose. The use of a gel permit easier application of the insulin and penetrant enhancer to the diabetic subject's

skin. In addition, it permits better control over dosage amounts. Finally, it maintains the components of the first layer in contact with a defined area of the subject's skin prior to application of the adherent, nonporous patch.

The amount of gel material employed may vary widely depending upon the identity of the gel material and the identity and amount of penetrant enhancer and carrier. In general, the amount of gel material will not exceed about 50% by volume of the first layer. In one preferred embodiment of the invention the gel material and penetrant enhancer each comprise about 33% by volume of the first layer.

The adherent, nonporous patch material may be any of the various such materials known to be useful as a patch. One example of such a patch material useful in the practices of this invention is polyethylene.

This invention provides a method of treating diabetes which comprises applying to the surface of a diabetic subject's skin a composition of the type described herein for suitable period of time, such as 1-12 hours, to permit insulin present in the composition to penetrate across the skin, enter the bloodstream and effect blood sugar levels.

The following examples are set forth to assist in understanding the invention but are not intended to, and should not be construed to, limit in any way the invention as defined by the claims which follow.

EXAMPLE 1

Bovine-porcine regular insulin (Eli Lilly and Company, Indianapolis, Indiana) was topically applied to the skin of streptozotocin-diabetic male BO.BR mice, beneath a polyethylene patch (Steridrape™ - 3M Company, Minneapolis, Minnesota), which was applied to the torso. Drug-skin contact occurred over approximately 1-2 cm^2 of body surface. Body hair was clipped 24-72 hours prior to each experiment. Mice were awake with free access to food and water. Animals were judged diabetic if they had more than three blood glucose values >400 mg/dl over at least 10 days. Blood glucose was measured by the glucose oxidase technique on tail vein blood (Ames dextrometer) [Jarett, R. et al., Diabetes 19:7234 (1970)].

Significant lowering of blood glucose was manifest within 2 hours and persisted for at least 4 1/2 hours. The effect was dose dependent, in that 100 units of regular insulin was effective, whereas 10 units was not. Controls receiving no treatment showed no reduction in blood glucose (Table 3).

Table 3

Effect of Topical Insulin on Blood Glucose of Diabetic Mice

				Blood Glucose <150. mg/dl		
Insulin	Patch	%DMSO	Gel	#	Onset(minutes)	Duration(hours)
—	+	—	—	0/5	0	0
—	+	50.	—	0/3	0	0
—	+	100.	—	0/3	0	0
—	+	33.	+	0/3	0	0
1 U Reg	+	50.	-	0/3	0	0
10 U Reg	+	—	—	0/8	0	0
10 U Reg	+	50.	—	4/8	140	2-3
100 U Reg	+	—	-	5/9	100	>4 1/2
100 U Reg	+	50.	-	8/13	60	3-4
100 U Reg	+	33.	+	5/5	30	>8
1 U NPH	+	33.	+	1/6	240	24
10 U NPH	+	33.	+	4/6	180	24
100 U Reg	-	50.	-	0/5	0	0
		%NDMS				
—	+	1.	-	0/13	0	0
1 U Reg	+	1.	-	2/5	150	3 1/2
10 U Reg	+	1.	-	6/10	90	3
100 U Reg	+	1.	-	10/10	90	2-3
10 U Reg	+	.05	-	2/6	90	3
100 U Reg	-	1.	-	1/5	60	1/2
100 U Reg	+	1.	+	3/5	140.	1-3
10 U Reg	+	1.	+	1/5	180.	24
10 U Reg	+	5.	-	2/5	60.	1-2
10 U Reg	-	10.	-	1/5	60.	1-2

To enhance drug penetrance of the skin, dimethyl sulfoxide (33% or 50%) (DMSO-Sigma) was mixed with insulin. DMSO added to 100 units of regular insulin resulted in reductions of blood glucose in 8 of 13 mice. DMSO alone had no effect on blood sugar.

Addition of 1/3 v/v 2.5% hydroxypropylmethyl cellulose (HPMC-Gonisol Ophthalmic Ointment, Cooper Vision Co.) converted the insulin-DMSO mixture from liquid to gel, enhancing convenience of insulin applications. 100 units of regular insulin plus DMSO plus gel maintained normoglycemia for 8 hours. Declines in blood glucose were observed in 4 of 6 mice treated with 10 units of NPH insulin in combination with DMSO and gel. One unit of NPH insulin plus DMSO plus gel was effective in 1 of 3 animals studied. Gel plus DMSO controls' blood glucose levels were stable and unchanged for more than 6 hours. Replacement of DMSO with n-decyl-methyl sulfoxide (NDMS), 0.05% or 1% in 40% ethanol (Cyclo Chem. Corp.) was equally effective in a dose-dependent fashion for 1, 10 and 100 units of insulin. NDMS alone had no effect on blood glucose. (Table 1)

Example 2

To better define the advantages obtained by utilizing a patch an experiment was carried out using the same protocol as in Example 1. 100 units of insulin plus DMSO or NDMS were applied to the torso of diabetic mice either under a polyethylene patch or without a patch. The results shown in Table 4 clearly establish the importance of the patch.

Table 4

Effect of Polyethylene Patch on Trans-Dermal Insulin Therapy in Diabetic Mice

	Blood Glucose (mg/dl)		
	Time Zero	1 Hour	2 Hours
100 U Insulin Plus DMSO (no patch)	375	284	253
	>400	246	>400
	392	318	383
	392	388	>400
	386	>400	368
100 U Insulin Plus DMSO Plus Patch	370	135	81
	333	77	24
	>400	221	194
	>400	42	24
	>400	194	98
	348	172	61
100 U Insulin Plus NDMS (no patch)	>400	368	>400
	388	356	237
	>400	126	>400
	>400	>400	>400
	>400	>400	392
100 U Insulin Plus NDMS Plus Patch	>400	284	177
	318	159	73
	381	159	71
	368	276	142
	388	194	105

Example 3

An experiment to establish the effect of topical application of insulin on serum insulin levels as well as blood glucose levels was carried out using 1% NDMS in 40% ethanol as the penetrant enhancer and a polyethylene patch. The results shown in Table 5 clearly show the increase in serum insulin levels obtained when a composition according to the invention is applied to the skin surface of diabetic mice.

Table 5

Effect of Dermal Insulin Plus NDMS on Serum Insulin and Blood Glucose of SZN Diabetic Mice

Group	Blood Glucose (mg/dl)		Serum Insulin (mg/ml)	
	Time Zero	1.5 Hours	Time Zero	1.5 Hours
Untreated Diabetic Controls	>400		0.0	
	>400		15.9	
	>400		0.01	
	>400		0.0	
1% NDMS Alone (no insulin) Plus Patch	>400	249		0.19
	>400	206		1.97
	360	>400		0.0
	>400	309		0.63
	>400	325		1.99
1% NDMS Plus 100 U Reg. Insulin Plus Patch	>400	138		7.95
	318	73		>20
	381	71		>20
	368	110		>20
	388	98		>20

WHAT IS CLAIMED IS:

1. A composition which when applied to the surface of a diabetic subject's skin is useful for treating diabetes comprising a first layer in contact with the skin surface and a second layer covering the first layer, the first layer including an effective diabetes-treating amount of insulin, an effective enhancing amount of a penetrant enhancer and a suitable carrier and the second layer comprising a suitable adherent, nonporous patch material.

2. A composition of claim 1, wherein the amount of penetrant enhancer comprises up to about 50% by volume of the first layer.

3. A composition of claim 1, wherein the penetrant enhancer is dimethyl sulfoxide, dimethyl acetamide, dimethformamide, n-decyl-methyl sulfoxide or a glycol derivative.

4. A composition of claim 3, wherein the penetrant enhancer is dimethyl sulfoxide.

5. A composition of claim 3, wherein the penetrant enhancer is n-decyl-methyl sulfoxide.

6. A composition of claim 1, wherein the suitable carrier is water.

7. A composition of claim 1, wherein the first layer is in the form of a gel and includes a gel material.

8. A composition of claim 7, wherein the gel layer includes hydroxymethyl cellulose, hydroxypropylmethyl cellulose or hydroxypropyl cellulose.

9. A composition of claim 7, wherein the gel material comprises up to 50% by volume of the gel layer.

10. A composition of claim 1, wherein the gel material and the penetrant enhancer each comprise about 33% by volume of the gel layer.

11. A composition of claim 1, wherein the nonporous patch material comprises polyethylene.

12. A method of treating diabetes which comprises applying to the surface of a diabetic subject's skin a composition of claim 1 for a sufficient period of time to permit insulin present in the composition to cross the skin.

13. A method of treating diabetes which comprises applying to the surface of a diabetic subject's skin a composition of claim 7 for a sufficient period of time to permit insulin present in the composition to cross the skin.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US85/00695

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC 3

A61K 37/36, A61/L 15/03

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	514/3, 424/28

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

CHEM. ABSTRACTS 9th and 10Th Collective Index Remington's Pharmaceutical Sciences Physician's Desk Reference, 1980.

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	JP, A Published, 10 April 1982, Niho Electric Ind. KK	1-13
Y	US, A Published, 11 March 1975, Lowey et al.	1,7-10, 12,13
Y	US, A Published, 05 September 1967 Chen et al.	1-13
Y	US, A Published, 08 September 1970 MacMillan et al	1-6, 10, 12 & 13
Y	US, A Published, 20 April 1976, Smith	1-6, 10, 12 & 13

* Special categories of cited documents: [15]

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
10 June 1985	24 JUN 1985
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	GStone

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